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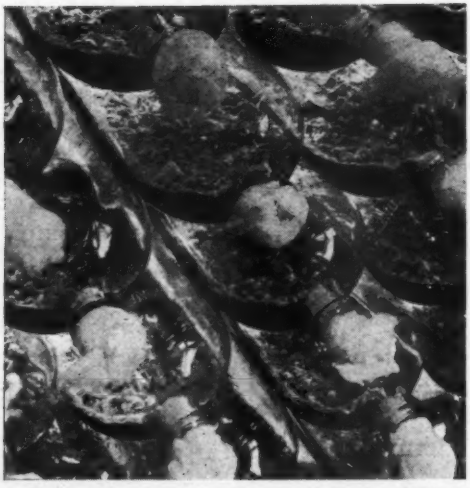

PENICILLIUM NOTATUM CULTURES
(See article reviewing present status of penicillin, p. 401)

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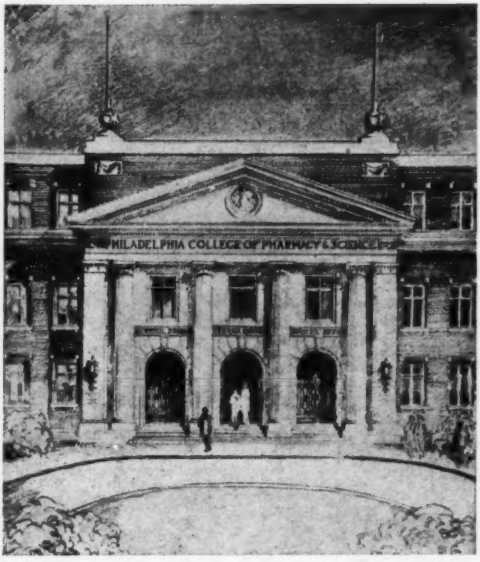

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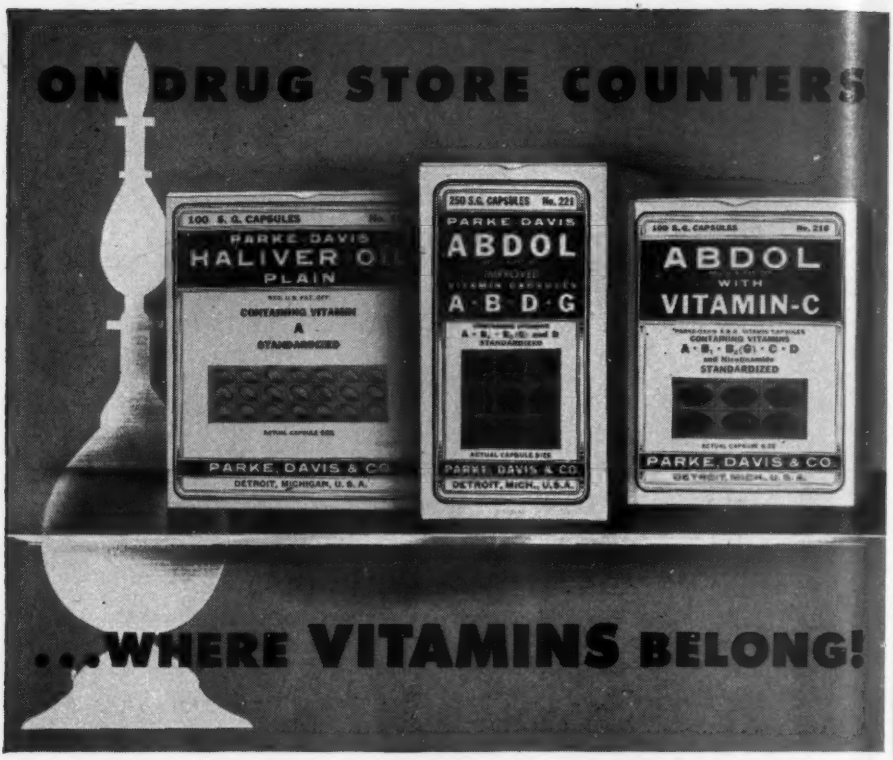

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IN MEMORIAM

PROF. DR. ROBERT EDER
1885–1944

DR. ROBERT EDER, Chairman of the Division of Pharmacy in the Swiss Federal Institute of Technology in Zurich, died from pneumonia on May 10, 1944. Born on August 8th, 1885, in Bischofszell, he graduated from the Gymnasium in Zug in 1904. He then obtained his practical pharmaceutical training in Basle from 1904-1906. This was followed by the academic pharmaceutical training at the University of Geneva and at the Swiss Federal Institute of Technology in Zurich, where he passed the State Board examination as an apothecary in 1909. After two more years of graduate work at the same institution he obtained the degree of Doctor of Science. From then on he dedicated his life work to the promotion of the sciences of pharmacy from a chemical viewpoint and with special emphasis on galenical pharmacy. As a young assistant in the pharmacy institute he took up research work, and with a paper "On the Commercial Chrysarobin," he was admitted to the faculty of the same institution. Soon afterward he became director of this well-known institution upon the death of his predecessor.

Dr. Eder was not only a well-known scientist but also an excellent teacher. His many publications in cooperation with graduate students fall into various categories: Pharmacognosy, plant chemistry, galenical pharmacy, synthesis of medicinals, pharmaceutical, toxicological and clinical analyses. With his work and enthusiasm he inspired many students. This was a life work in itself, but he also was very active as a member of the Swiss Pharmacopœia Committee. He later became vice-president of that Committee. In that capacity he again showed his ability for organization and administration. He represented Switzerland at the second international conference at Brussels, and he also represented his country as a member of the Technical Commission of Pharmacopœial Experts of the League of Nations. It was through this work that he made many contacts with professional men of all other countries and he enthusiastically cooperated in the Fédération Internationale Pharmaceutique. It filled his heart with deep regret and sorrow that these connections were so brutally torn apart by the World War. He did not live to see this war ended and to take up the good work again which he had started so successfully.

E D I T O R I A L

N. A. R. D.—A. PH. A. COOPERATION, A PROGRESSIVE STEP

FOR many years one of the chief weaknesses of organized Pharmacy has been the distinct cleavage between its professional and commercial interests. Pharmacy is unique among the professions in that a considerable amount of business acumen is required in order to successfully conduct an establishment wherein the public's needs may be served. In most other professions the services of the practitioner are the only items for which a charge is made and no large stock or supply of materials need be carried as in pharmacy. This situation in pharmacy has caused great difficulty, since the retail pharmacist must of necessity be both a professional as well as a business man. If his balance becomes somewhat displaced on the commercial side he is at once denounced by the ultra-scientific group of his profession, and if he becomes too scientifically inclined he is often endangered by bankruptcy. Under such circumstances it is small wonder that both difficulties are frequently encountered amongst retail pharmacists.

This condition has been aggravated by the advent of highly efficient merchandising groups known as "chains" leading many individual pharmacists into greater and greater depths of commercialism as a means of self-preservation.

The American Pharmaceutical Association has for years tried to represent the scientific and professional aspects of pharmacy and it has done so to an admirable degree. Using as its model other professional organizations, there has been little place in its activities for the business problems that confront retail pharmacists. The National Association of Retail Druggists, by protecting these business interests of the pharmacist, has grown in power and prestige with the druggists of America. For too long each organization went its own way recognizing each other's sphere of influence and activity but rarely trying to act in a joint manner. The result has been that the A. Ph. A. almost ignored the commercial aspects of pharmacy and the N. A. R. D. was not sufficiently professionally minded. Such a sad state of affairs was harmful to not only both organizations but to the phar-

macist as well. Like it or not, he could ill afford to ignore either group, thereby suffering as does a child with dissenting parents.

Then came the war and many of the weak spots in our national life began to creak and groan. Pharmacy's lack of well-oiled machinery caused many an anxious moment and many a sad defeat. Then it was that our leaders saw the urgent necessity of united action for the good of pharmacy. Last year a great step forward was taken when the first joint meeting of the Executive Committee of the N. A. R. D. and the Council of the A. Ph. A. was held in Washington. The meeting was one of real accomplishment and for the first time these two great organizations embarked upon a program mutually agreed upon for the benefit of all pharmacy. This year the second meeting of this Joint Committee was recently held in Chicago, and the agenda of the meeting indicates that practically every major problem in pharmacy was considered and a program mapped out for facing them.

Secretary Dargavel of the N. A. R. D. and Chairman Fischelis of the Council of the A. Ph. A. each deserve credit for the accomplishments of this meeting as does every member participating.

There are many things in pharmacy today to cause one concern, but with our key organizations working at last in harmony the future is immeasurably brighter. Once again we can appreciate that intelligent compromise and teamwork is the shortest road to maximum achievement. If pharmacy and pharmacists are ever to have the prestige and respect that is so well deserved, unity of action toward a common goal must be the objective of each of its many organizations. The surest way to lose a ball game is for each member of the team to play against his fellow-teammates as well as his opponents. Joint action by the A. Ph. A. and N. A. R. D. demands the support and praise of every pharmacist in the United States.

L. F. Tice

THE MICROBIOTICS*

By John N. McDonnell, D. Sc.**

ALTHOUGH very new and little understood, the microbiotic drugs present one of the most striking developments in the history of the health sciences. Within half a decade, an entirely new therapeutic concept has been instituted. An important new group of efficacious drugs has been made available to the medical profession for the eradication of disease.

Many scientists believe, however, that the surface of this new subject literally has only been touched. The microbiotic drugs, and certainly those best known at this time, have far greater possibilities than are appreciated at present.

Nomenclature

From a technical viewpoint, the term "microbiotics" is a misnomer, when applied to the group of chemotherapeutic agents derived directly from microorganisms. Other descriptive names have been proposed, such as "antibiotics" and others. None of these names is adequate, but for the present they are accepted.

Since the days of Pasteur and Koch in the infancy of bacteriology, the "biological products" have been the accepted mode of therapy in the prevention and treatment of diseases caused by pathogenic bacteria. Serums and vaccines, toxins and toxoids, and antitoxins have been developed containing, or designed to create, natural antibodies by means of which a patient may be "immunized" or protected against a pathogenic bacterial infection, or by means of which an infectious disease may be successfully treated. In the past, these natural products have satisfactorily served to reduce the incidence and mortality of certain contagious bacterial and virus-caused diseases. However, they have been ineffectual against many conditions and in particular against diseases caused by protozoa.

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* Presented before the Fifty-eighth Annual Convention of Association of Science Teachers, Middle States Association of Colleges and Secondary Schools, New York, November 25, 1944.

** Chief, Research and Statistics Unit, Drugs and Cosmetics Branch, Chemicals Bureau, War Production Board, Washington, and Director of the War Production Board's Civilian Penicillin Distribution Office in Chicago; Assistant Professor in Pharmacy, Philadelphia College of Pharmacy and Science; Editor of *"American Professional Pharmacists"* and of *"El Farmaceutico"*; Format Editor, *"Medical Times."*

Chemicals in Therapy

The application of chemical agents to the combating of disease of course is no new development. To a degree, chemicals had been included in the armamentarium of the "medicine man" since time immemorial. The magnificent charlatan, Paracelsus, was the first real exponent of chemicals in therapy. Little was contributed to this field of medical science for hundreds of years, until the discovery of the alkaloid, quinine, in cinchona early in the last century by the pharmacists, Pelletier and Caventou, and the isolation of emetine from ipecac. These substances were the first chemical agents effective against the plasmodium of malaria and against amebic dysentery. They represented the beginnings of "chemotherapy", differing from "chemicals in therapy".

Chemotherapy

Chemotherapy had its true beginning in 1870, when the Frenchman Lavaran traveled to Africa in search of a chemical substance which would prove of value in the treatment of trypanosomal diseases such as malaria and sleeping sickness. Choosing arsenic from among the heavy metals, Lavaran successfully developed the arsanilates, and for his biochemical discoveries was the recipient of the 1903 Nobel prize. Ehrlich and Robert Koch went further in his researches. From their work came salvarsan and neoarsphenamine. These were the first potent agents against the protozoan disease, syphilis.

Other than the discovery of the arsenicals, there were no striking advances in chemotherapy until Hoerlein's researches in 1910, in the use of certain sulfonamide-substituted azo dyes. Even he failed to recognize the value of his discovery.

Therapeutic Index

It must be remembered that the value of a chemotherapeutic agent against disease is determined by what is known as the *"therapeutic index"*. Pharmaceutical research workers use the mathematical ratio of *"high killing power on bacteria or protozoa causing disease"* as the numerator of a fraction, the denominator of which is *"low toxicity or killing power on animals and patients"*. Thus many chemicals would be effective against pneumococci of pneumonia or in combating the organisms causing some other disease, but at the same time they would probably kill the patient. The higher the killing power against microorganisms and the lower the toxicity,—the better the drug.

Sulfonamide Drugs

Until Domagk, twenty-five years later, experimented with one of the azo dyes developed by Hoerlein, the value of the sulfonamides in the treatment of bacterial infections lay undiscovered. The story of the "sulfa drugs" is now well known, and the layman is fairly familiar with sulfanilamide, sulfathiazole, sulfadiazine, and even with those not so well known. Many hundreds of different *"sulfa drugs"* have been developed and tested in laboratory and clinical trial, but only a few superior ones have been approved and chosen for production. Those which have been employed in the fight against disease have caused a material change in health care and have added nearly a decade to the life span of man.

What is well understood by medical and pharmaceutical workers, and now appreciated even by the general public, is that the "sulfas" are by no means harmless; they are more or less toxic in nature. Some individuals are "sensitive" to them, showing toxic reactions when they are administered, while it is also possible for a patient to develop this sensitivity. In addition, there are not infrequently individuals who prove "resistant" to the drugs. In other words, there is a percentage of cases of many of the customarily sulfonamide-amenable diseases where the infection is resistant to sulfonamides. Also, the "sulfas" are not of value in the treatment of protozoan infections.

The primary over-enthusiasm for the sulfonamides has subsided, and we now fully appreciate their proper place as potent, efficacious specifics. While they are not a general panacea for all bacterial diseases, they are exceedingly useful against a selected group of infections.

The search for other and better drugs went on, with the emphasis upon those which have as their mode of action a direct toxic effect or metabolic inhibitory effect on the offending organisms.

Antibiotic Concept

Through the years there existed another concept of antibacterial action in the treatment of disease. As long ago as 1877, when Pasteur and Joubert conducted their immortal experiment on anthrax, they had observed that cultures of anthrax ceased to grow when accidentally contaminated by air bacteria. They also observed that sheep survived when infected with this contaminated culture. This was the first evidence that a substance produced by one microorganism is capable of arresting the growth of another. Even though Pasteur

called attention to this apparent principle, he failed to pursue it further.

At one time it had been believed that the soil was the source of all infections and epidemics. Koch's experiments in 1881 on the survival rate of bacteria showed that pathogenic organisms die out rapidly in the soil, due to some unknown factor present in soil.

The potentialities of antagonistic mechanisms among the microorganisms were appreciated by Cantani, who in 1885 endeavored to treat certain diseases by means of known cultures of saprophytic organisms.

Pyocyanase

Later, many other "antibiotics" were discovered, including extracts from *Bacillus pyocyaneus*. Pyocyanase has been known since the early "nineties", although it was never deemed very effective. It was never obtained in crystalline form, and was employed chiefly in experimental studies, although in Germany since 1930 a pyocyanase ointment has been available for local application on skin lesions resulting from anthrax.

The last step in the series of basic researches which preceded the advent of the recent antibiotic studies was when Vaudremer attempted to treat tuberculosis with *Aspergillus fumigatus* cultures. His unsuccessful work followed preliminary laboratory *in vitro* tests which had given great promise.

Accidental Discovery

Our story really begins, however, in 1928 in the bacteriology laboratory of St. Mary's Hospital, in London. During the routine examination of some culture plates Professor Alexander Fleming observed entirely by accident a contaminating mold which caused lysis of the staphylococcus organisms nearby. He had observed a phenomenon which had been ignored by countless bacteriologists before and since. Fleming subcultured the mold in broth and found that a strong antibiotic, nontoxic to animals, passed into the broth from the mold. The broth apparently possessed marked inhibitory, bactericidal and bacteriolytic properties. Fleming coined the name "penicillin" to designate a filtrate of the broth culture of the particular organism which he incorrectly identified as *Penicillium rubrum*. The term "penicillin" has been retained, and while medical dictionaries recommend the pronunciation as "pen-iss-lin", the majority of scientific workers prefer to use "pen-i-sill-in".

After a year's study, Fleming established the specific activity of penicillin against various gram-positive microorganisms highly pathogenic to man, including the streptococci, staphylococci, gonococci, pneumococci and meningococci. He had also discovered that the filtrate was ineffective against many gram-negative cocci and bacilli.

Identification

In 1932 other British workers, Clutterbuck, Lovell and Raistrick, verified Fleming's experimental reports and with the cooperation of the noted American mycologist Thom, correctly identified the mold as *P. notatum* Westling. Fleming continued his studies but contented himself with reporting that it did not disturb human white blood cells, and that it appeared to have some value for local treatment of dermatologic infections. He employed the filtrate chiefly to inhibit contaminants in the isolation of organisms insensitive to penicillin, such as *Hemophilus influenzæ*.

Clutterbuck in 1932 attempted to isolate the active principle from the penicillin filtrate but failed, and with Fleming's reluctant agreement concluded that the substance was too labile. Thus, except for occasional use as a differential culture, Fleming's discovery lay dormant for ten years.

Lysosyme

In 1929, the year of Fleming's first report, another British investigator, Howard Florey, and his associates at Oxford began work on lysosyme, an antibiotic substance discovered seven years before by Fleming, and ultimately crystallized in 1937 by Roberts. During the next decade Florey continued his progress, firmly convinced that somehow an antibiotic would be discovered that would be non-toxic to man yet of value in the treatment of infections. The mechanism of these substances was not clearly indicated, but the principle upon which they acted was generally accepted. Florey studied many organisms but to no avail, until 1938 when he directed his attentions to penicillin.

Soil Bacteria

During this period, other equally striking work had been conducted in the United States. In the course of studies at the Rockefeller Institute for Medical Research in New York, on the virulence of different types of pneumococci, Dubos in 1938 completed a successful search for a specific bacterial enzyme which by decomposing

the capsular polysaccharides of the organisms would render the pneumococci avirulent. He believed that microorganisms existed which would attack other unrelated microbial cells, assuming that all organic matter added to the soil eventually is decomposed by soil microorganisms. Dubos hoped that living cultures added to soil would develop selective flora capable of attacking certain bacterial species. He was successful in isolating such a material, and prepared from it three active substances inhibitory to gram-positive organisms. They were *tyrocidine, gramicidin* and *gramidinic acid.*

Tyrothricin, Tyrocidine and Gramicidin

Tyrocidine hydrochloride was first termed graminic acid. A crystalline neutral substance was found to be gramicidin, while gramidinic acid later was found to consist of gramicidin and tyrocidine, and was called by the term now employed, namely *tyrothricin.* All were markedly bactericidal *in vitro* against gram-positive microorganisms, but tyrothricin and tyrocidine were also effective against organisms of the gram-negative group.

Gramicidin proved to be most effective, but caused serious toxic reactions. However, the highly bactericidal effect of gramicidin when injected into experimental animals previously inoculated with cultures of various organisms revived interest in Fleming's penicillin.

Accordingly, Florey the biochemist and his Oxford associates, men whose names have since become renowned for their outstanding work, began the systematic study of the new substance, penicillin. Abraham and Chain, and Heatley, all chemists, together with Lady Florey, a physician of competence who was the major contributor to studies on local use of penicillin, all reported on phases of the work.

The Culture

The crude fluid first prepared as an extract of the culture broth of penicillin showed remarkable properties. One part in several hundred thousand and even up to one in a million dilution inhibited growth *in vitro* and *in vivo,* of a number of organisms. It was apparent that here was a potent new agent with, to quote Florey in 1941: ". . . the bacterostatic power . . . as great as, or greater than that of the most powerful antiseptics known, such as the heavy metal compounds, the acridine derivatives, etc." The causative agents of anthrax, gonorrhea, pneumonia, meningitis, gas gangrene, and a

host of other diseases and infections one by one yielded to this new miraculous substance.

Problems

As yet, the product was not ready for use in the treatment of disease in humans. Two problems confronted the research workers. How should the active substance be extracted? How should it be standardized?

The identification of the physical and chemical nature of the active principle could await the satisfactory resolution of these two earlier perplexing problems, even though the analysis and synthesis of the principle was a task which was of terrific magnitude.

The Oxford Unit

A test for potency was ingeniously worked out by Heatley, under Florey's direction. Fleming's original serial dilution method, similar to that employed in usual bacteriologic procedures, was empiric and unsuited for exacting work. A modification was developed, using porcelain cups set on agar plates. Heatley defined the "Unit" of penicillin antibacterial activity for the cup method as that amount of penicillin which when dissolved in 1 cc. of water gives a zone of inhibition 24 mm. in diameter, or the amount by serial dilution which when dissolved in 50 cc. of broth completely inhibits the growth of a test strain of *S. aureus.*

The "unit" of penicillin was accepted by most workers and was named in honor of Florey. However, the latter modestly disclaimed the tribute and proposed instead the now generally accepted "Oxford Unit", after its place of discovery. This term is still in use in this country, but because its measure is so small, about 0.6 microgram of penicillin, and because so many are represented in usual therapeutic procedure and industrial production, the British have invented the term "mega-unit" to indicate one million Oxford units.

In this country and in England over a score of research laboratories are collaborating in a study of penicillin assays under United States Pharmacopœial and Food and Drug Administration sponsorship, in order to develop standardized and improved methods.

Extraction

The first method of production employed was the "bottle" process, where bottles, flasks or trays were used, requiring thousands of con-

tainers to yield any appreciable quantities of the broth culture. This was the "sure" method and the one employed by all producers in their early programs. Other methods developed later in this country were the "trickle" method, where inoculated broth flows over stones or chips as an adaptation of the "quick" vinegar process, and the "bran" process, where sterile bran is inoculated by cultures, and the penicillin extracted later.

Penicillium notatum grows under both surface and submerged conditions, although different strains are used for the differing processes. The "submerged" or "deep tank" method which is responsible for most of present-day production allows the penicillium inoculated sterile broth to be aerated for the period of the fermentation cycle, in thousand-gallon tanks or larger.

The solution to the problem of extraction, which had impeded progress for over a decade, was discovered soon after the unit was developed. It involved the passing of impure acid penicillin broth (pH 2 to 3) from a watery solution into an organic solvent such as ether, chloroform or amyl acetate, and the subsequent passage of the purified agent again into water, shaken with alkali. This principle, by appropriate cycling and with the aid of further steps in purification with activated carbon, followed by the snap-freezing and desiccation procedure employed in processing blood plasma, still holds in industrial practice, with some modifications from plant to plant.

Clinical Trial

A minute quantity of partially purified penicillin was finally obtained, and in England on February 12, 1941, the first human patient was treated. The response was dramatic and extraordinary, even beyond the optimistic hopes of the research team. However, just as its full powers were in evidence, the supply of the drug became exhausted; the patient had a relapse and died. Additional supplies were prepared, and by June half a dozen other patients had been treated, even though the Oxford workers had considerable difficulty in finding subjects. Those eventually turned over to the penicillin team were generally moribund, the most difficult of all possible conditions, where the attending physicians believed that the experimentation could not hurt the patients for whom all hope had already been abandoned. Every one responded, although twice at the peak of success the drug supply again ran out and the patients died.

American Interest

Faced by all kinds of operational difficulties, shortage of manpower, lack of equipment and a wide general apathy to their reports, the English research workers remained undaunted. Under the auspices of the Rockefeller Foundation, they came to America, and Florey and Heatley presented their appeal for technical and industrial help to the National Research Council in Washington early in July of 1941. Through the Summer months of that year Florey and his associate worked under grants from these bodies and with the research and production staffs of several enterprising American pharmaceutical and chemical houses. They gained the cooperation of Coghill and his co-workers of the U. S. Department of Agriculture Experiment Station at Peoria, experts in the fermentation field. They were able to develop new culture methods and to find ways of increasing yields. Florey returned to England in September of 1941 to devote his efforts to the improvement of the purification process. Heatley, his fellow worker, remained in this country for a year and assisted in the planning of the first small program of production.

The results obtained in these early months' experiments were even more startling than Florey and Heatley had dared to predict or to hope. American research workers under the direction of the Office of Scientific Research and Development found that their observations more than bore out the early promise of the drug. With renewed enthusiasm, larger scale production of the drug was planned.

In the interim the United States was plunged into war, but nothing was allowed to interfere, and the development work proceeded unabated.

Clinical Studies

The first patient to be studied in this country under the extensive research program which has been in force since was treated with penicillin on March 14, 1942, in New Haven, Conn. An advanced case of hemolytic streptococcus septicemia, the response was immediate. A few months later, when additional small quantities of the drug made available from the laboratory scale production began to provide ample evidence of the almost miraculous powers of this new therapeutic agent, the several cooperating pharmaceutical firms came to the War Production Board with appeals for priority assistance to obtain the exceedingly critical equipment and materials needed for their

new pilot plants, which were the next step from research to industrial production.

Approximately fifty different chemical and other substances are required for the preparation of inoculum, culture media, recovery and testing. Among these are lactose, starch, talc, activated carbon, several acetates, ether, chloroform, lime, sulfuric acid and a by-product of starch manufacture, corn steep liquor. Several of these substances are consumed now in quantities totalling millions of pounds a year. The containers and tanks, piping, gauges and meters, vacuum and pressure pumps, refrigeration and sterilization apparatus have represented millions of dollars' worth of war-time critical material. However, immediate cooperation was extended, and one of the most dramatic stories of war production was under way.

Complement

Penicillin is not a panacea or a "cure-all". It is an effective therapeutic agent and a complement to the sulfonamide drugs. It has some advantages over the latter, but may never replace them. However, medical history will record the coming of penicillin as an important milestone, for this safe drug has proved effective against many pathogens which heretofore proved immune to chemotherapy, and against infections which had shown an all-too-high lethal rate despite amenability to available therapeutic measures. The list of such organisms and infections is impressive and broader clinical investigation will find even greater importance for the new drug just as it is discovering numerous infections against which it is valueless.

Advantages

Four theoretical advantages of penicillin over the sulfonamides, however, are: (1) it is more potent in inhibiting growth of organisms; (2) its bacteriostatic power is influenced to only a minor extent by the number of organisms; (3) it is not antagonized by breakdown products of tissue autolysis or by exudates (pus); and (4) it is nontoxic.

Penicillin is dramatically effective against a host of "killers": meningitis, pneumonia, tetanus, anthrax, osteomyelitis, syphilis, empyema, cellulitis, diphtheria, gas gangrene, relapsing fever, actinomycosis, puerperal sepsis, and many others. In the treatment of war wounds, penicillin first proved its worth on the bloody sands of North

Africa, from whence came the early reports to our Army medical staff which prompted them to experiment with it. Out of these studies came the Army's demand last year for penicillin,—and as much of it as it was possible to produce! Since then penicillin has earned for itself the equivalent of the Congressional Medal of Honor, for thousands of service men's lives have been saved by its wonderful powers, and countless crippled and infected bodies quickly restored to health and usefulness. From the mysterious but important realm of war medicine penicillin emerged as a "miracle drug" for soldiers and sailors and for civilians alike. However, penicillin is by no means the only successful or promising antibiotic.

Classification of Antibiotics

There are many antibiotics. While it is a simple matter to classify antibiotic substances after their chemical structure has been clarified, certain criteria have been developed to enable workers to properly evaluate these agents. The criteria, according to Waksman, are: (1) The organism that produces the substance; (2) The toxicity of the substance and its chemotherapeutic activity; (3) The selective effect of the material upon specific bacteria. (This is termed the bacteriostatic or antibiotic spectrum); (4) The chemical nature of the substance. (Long before the active substance is isolated, microbiologists have a fairly good idea as to its general character); and (5) The mode of action of the substance upon bacteria.

Since an organism may produce several different antibiotics, and in turn several different organisms produce the same type of antibiotic, duplication has been discovered. For instance, a dozen organisms produce penicillin, while clavacin, patulin and claviformin from different organisms are the identical substance.

Aside from the several known isomers of penicillin, there are a number of other antibiotic agents which deserve mention. Of those which have been mentioned to any extent in the literature, only a few are worthy of comment here.

Tyrothricin

Tyrothicin, the combination of gramicidin and tyrocidine, is a highly complex chemical of varying composition obtained from cultures of the aerobic, spore-forming soil bacteria, *Bacillus brevis* strain BG. Its chemical structure is $C_{44}H_{63}N_9O_{11}$ or $C_{74}H_{106}N_{14}O_{14}$.

Available as a commercially-marketed product, it is used in diluted isotonic solution by instillation, irrigation or wet dressing. It may be introduced into the body cavities such as the pleural cavity, sinuses, mastoid and urinary bladder. It is exceedingly toxic in the bloodstream and is not indicated for parenteral injection or oral use. Tyrothricin has found particular value in treatment of indolent ulcers, abscesses of skin and mucosa, mastoiditis, certain infections of eye, nasal sinus and pleural cavity, empyema, postoperative infections and osteomyelitis. It has been found most effective against certain species of staphylococci, streptococci, and similar organisms.

Gliotoxin

Gliotoxin was crystallized several years ago, before penicillin, from *Gliocladium fimbriatum, Aspergillus fumigatus* and Trichoderma species. It is effective against both gram-positive and gram-negative organisms but is too toxic for therapeutic use. Its chemical formula is $C_{13}H_{14}O_4N_2S_2$. Gliotoxin has been found to be effective against the staphylococci, streptococci and *Diplococcus pneumoniæ*.

Fumagacin, Fumagatin and Aspergillic Acid

Aspergillic acid is a substance derived from *Aspergillus flavus,* having the chemical structure of $C_{12}H_{20}N_2O_2$ without sulfur in the molecule. It has a limited range of effectiveness against both gram-positive and gram-negative bacteria.

Fumagacin, or helvolic acid as it is also called, is similar in action to penicillin. It has an indefinite chemical formula with either 32 or 53 carbon atoms, and is lacking in both nitrogen and sulfur. Being water-insoluble in nature and less active, it is less valuable even though it is generally effective against gram-positive organisms, similar to the action of penicillin. It is derived from *Arpergillus fumigatus.* Also obtained from the same organism is fumagatin, $C_8H_8O_4$, which has limited sensitivity and therapeutic value.

Other Ketone Compounds

These ketone antibiotic compounds have been crystallized and obtained in pure form. Several others are of lesser significance, such as *penicillic acid* ($C_8H_{10}O_4$) from *P. cyclopium* and *P. puberulum; kojic acid* ($C_6H_6O_4$); *puberulic acid* ($C_8H_5O_6$); and *puberulonic acid* ($C_8H_4O_6$).

Clavacin

A significant ketone antibiotic is clavacin, which has many aliases, such as *patulin, claviformin* and *clavatin.* Obtained from *Aspergillus clavatus, P. patulum* and *P. claviforme,* it has the formula $C_7H_6O_4$. Great enthusiasm was evidenced some months ago in Great Britain because of its reported value against both gram-positive and gram-negative organisms and for its apparent action upon the secondary organisms which complicate the common cold. Later experimental use by other workers failed to substantiate the early expectations that it would prove a specific for the common cold, but the subject is still an open one with many authorities, according to Raistrick.

Chaetomium cochliodes is the source of *chætomin,* which has also been isolated but never purified. It has limited usefulness, if any. Citrinin, $C_{13}H_{14}O_5$, is a quinone from *P. citrinum* and from other species of aspergillus. It is not as active as the other antibiotic agents and is more toxic.

Actinomycin

Of the various species of organisms from which antibiotics may be developed, the actinomyces are the most promising, for over one-fifth of all of these species are capable of producing antibiotic substances of some type.

One of the most promising of the group is *actinomycin A.* Obtained from *A. antibioticus,* it is a pigmented ring compound with the formula $C_{41}H_{56}N_8O_{11}$. Although it is toxic to animals, its complex nature provides possible avenues of approach whereby the chemist may substitute in the formula and bring about a reduction in toxicity and a further increase in physiologic activity.

Various actinomyces species produce *actinomycetin,* a polypeptid of indefinite composition which is comparatively non-toxic but of only limited activity. It acts more or less as a proteolytic enzyme.

Notatin

Penicillin B, notatin and *penatin* are terms used to describe a glucose aerohydrogenase from *P. notatum.* It has only slight activity and specificity against a limited number of organisms. None of this entire group of antibiotics, with the exception of penicillin and tyrothricin concentrate, have achieved sufficient recognition to warrant commercial production for therapeutic use.

Streptothricin and Streptomycin

However, another new antibiotic which is already in the clinical research stage of development is streptothricin. This substance is derived from *A. lavendulæ* and is effective against both gram-positive and gram-negative organisms. It possesses the properties of an organic base. Streptothricin is antimicrobic rather than merely antibacterial for it has shown value against various pathogenic fungi and higher forms. In addition to equaling the value of penicillin against gram-positive organisms (with the exception of streptococci), it has a significant value against such gram-negative organisms as the colon-typhoid and salmonella groups. This presages a possible future use in the treatment of infected wounds and burns.

Streptomycin, a closely related compound, is similar in activity and lack of toxicity, with particular value in animal diseases such as fowl typhoid and brucellosis.

As far as the related antibiotics are concerned, three substances are now recognized as valuable in the treatment of human infections. One is derived from soil bacteria, the other two from molds. Tyrothricin has sufficient value to be retained as a therapeutic agent for immediate non-tissue penetration contact bactericidal action, particularly for operational usage. Streptothricin may prove of value in the future for its effectiveness against the gram-negative organisms. Penicillin will still remain the drug of greatest promise, at least until some as yet undiscovered substance appears to displace it.

Penicillin Therapy

To return to the subject of penicillin, a pertinent fact concerning its action is that, just as certain sulfonamide-fast bacteria are sensitive to penicillin, so there has been reported evidence of organisms which are persistently resistant to penicillin. The cause may be natural, acquired by prolonged contact, or due to small colony variants. So far as is known, no cases have been reported yet where a sulfonamide-fast organism has proven resistant to penicillin, and *vice versa,* which is gratifying.

Any list of pathologic conditions and states in which penicillin was known or believed to be effective must of necessity be considered incomplete. Certainly present research programs, and the results which will be gained from usage of the drug when penicillin is available in less limited quantities than at present, will undoubtedly broaden

its field of indications. It is already evidenced that where it is equally as efficacious as other measures, including sulfonamides, economic factors and mode of administration govern usage.

A concise and helpful report on indications for penicillin was prepared by Dr. Chester Keefer, chairman of the committee on chemotherapy of the National Research Council, and consultant to the Office of Scientific Research and Development, for the War Production Board's Office of Civilian Penicillin Distribution. Based on accumulated experience, it was found that penicillin was the best therapeutic agent available for the treatment of certain conditions, as follows:

> "All staphylococcus infections with and without bacteremia: Acute and chronic osteomyelitis, carbuncles—soft tissue abscesses, meningitis, cavernous or lateral sinus thrombosis, pneumonia—empyema, carbuncle of kidney, wound infections—burns, and endocarditis.
>
> "All cases of clostridia infections: Gas gangrene, malignant edema.
>
> "All hemolytic streptococcic infections with bacteremia and all serious local infections: Cellulitis, mastoiditis with intracranial complications, i. e., meningitis, sinus thrombosis, etc., pneumonia and empyema, puerperal sepsis, peritonitis and endocarditis.
>
> "All anærobic streptococcic infections: Puerperal sepsis.
>
> "All pneumococcic infections of meninges, pleura, endocardium. All cases of sulfanamide-resistant pneumococcic pneumonia.
>
> "All gonococcic infections especially those complicated by arthritis, ophthalmia, endocarditis, peritonitis, epididymitis. All cases of anthrax; chronic pulmonary suppuration in which surgical treatment is contemplated; all meningococcic infections failing to respond to sulfonamides; all cases of bacterial endocarditis due to susceptible organisms."

Originally listed in a second group, where penicillin has also been found effective, but its position not definitely defined, were syphilis, bacterial endocarditis and actinomycosis. It is now generally recognized that the former bacterial endocarditis is a proper indication for penicillin therapy. Recently added was diphtheria, especially in horse serum sensitive patients.

Keefer listed in a third group certain conditions of questionable value, in mixed infections of the peritoneum and liver in which the predominating organism is of the gram-negative flora, such as rup-

tured appendix, liver abscesses, urinary tract infections and in rat bite fever due to streptobacillus moniliformis.

Penicillin was contra-indicated (meaning that the drug was of no value and where administration might cover up symptoms or forestall other proper therapeutic measures, not that any danger was present from toxicity) in the following cases because it is ineffective:

> "All gram-negative bacillary infections: Typhoid—paratyphoid, dysentery, E. coli, H. influenza, B. proteus, B. pyocyaneus, Br. melitensis (undulant fever), P. tularense (tularemia), B. friedlander;
>
> "Tuberculosis, toxoplasmosis, histoplasmosis, acute rheumatic fever, lupus erythematosis diffuse, infectious mononucleosis, pemphigus, Hodgkins' disease, acute and chronic leukemia, ulcerative colitis, coccidiomycosis, malaria, poliomyelitis, blastomycosis, non-specific iritis and uveitis, moniliasis, virus infections, cancer."

Administration

Penicillin must be administered in rather large doses at first to create a satisfactory blood level, and repeated administration is required thereafter at four-hour intervals or continuously because it is readily excreted and only sparingly absorbed. One of the drawbacks of penicillin therapy is the necessity for parenteral administration. The drug is inactivated apparently when administered orally. However, it has been reported that if large enough quantities are given orally, adequate blood levels may be attained.

Penicillin is supplied in ampuls and vials of 100,000 Oxford units each, and when kept at refrigeration temperature will retain its potency for over a year. Inasmuch as penicillin is soluble, it may be dissolved in small amounts of sterile, distilled, pyrogen-free water, or in sterile, normal saline solution. When large unit sizes are being used in hospitals, the contents of the vial should be dissolved so that the final concentration is 5,000 units per cc. This solution should be stored under aseptic conditions in the ice-box. While it should be made freshly every day, Kirby has reported that solutions will retain their potency for a week, and even when allowed at room temperature it was found that potency remained for more than a day.

For intravenous use the dry powder is dissolved in sterile physiological salt solution in concentrations of 1,000 to 5,000 units per cc. for direct syringe injection. It may dissolved in sterile saline or 5

per cent glucose at 25 to 50 units per cc. for constant intravenous therapy. For intramuscular injection the total volume of individual injections should be small, i. e. 5,000 units per cc. of saline. For topical application, solutions in salt solution of 250 units per cc., with the volume increased to 500 units per cc. where resistant or intense infections appear. The powdered form is irritating to wound surfaces and should not be used.

Romansky and Rittman recently reported on the use of a sterile mixture of 4 per cent beeswax in peanut oil as a base for penicillin. This prolongs and increases absorption, maintaining penicillin levels for as long as eight hours. Greater economy and effectiveness may be attained by such measures if they prove practical.

There are three common methods of administration for penicillin: intravenous, intramuscular, and topical. Subcutaneous injections are painful and should be avoided. Repeated intramuscular injections may be tolerated less well than repeated or constant intravenous injection, but frequently the intramuscular route is the method of choice.

The dosage of penicillin varies from one condition to another, and depending upon the patient. The objective is to bring the infection under control as quickly as possible.

Processes

The production of penicillin by several basic processes has been engaged in by over a score of industrial firms. In all of these pure culturing and aseptic handling is essential. Where contamination occurs the penicillium fails to produce penicillin. From seed culture stage to large volume production either by flasks or deep-tank method is a step which has tasked the ability of the entire industry. The details of the processes vary from one process to another and need not be discussed here. Suffice to say that the final product is a sterile dry yellow to brown powder. It is a relatively impure product, marketed for civilian use as the sodium salt, although considerable quantities of the calcium salt are being made available for research purposes and for the use of the armed services.

Potency

The present penicillin product has a potency of more than 1,000 Oxford units per milligram, and it is rapidly approaching chemical purity, the potency for which has recently been agreed upon at the

meeting of international experts on penicillin in London under League of Nations sponsorship, as 1,650 Oxford units per milligram. It has been observed that the purer the product the less likelihood of reactions, and while some of the pure salt has been prepared, mostly for use as a reference standard, clinical trial has not yet determined whether any therapeutic value is lost in the complete purification process.

Recent work on penicillin has indicated that there are at least three types of penicillin: penicillin F (British "I"), penicillin G (or "II") and allopenicillin ("III") or factor X, a more stable, more readily crystallizable and perhaps more clinically effective substance. Wintersteiner isolated pure crystalline penicillin, but the search for its chemical identity and for methods of syntheses remains shrouded in wartime secrecy.

Production

The dramatic story of the battle for production of penicillin must also await the end of the war for the telling. However, it may be stated that only 400 million units of penicillin had been produced experimentally prior to June of 1943, and little more than 20 billion units during the balance of the year. Now, twelve months later, twenty tremendous plants located from coast to coast are pouring out increasing quantities of the drug. They represent an investment of almost thirty millions of dollars in critical equipment and materials. During the month of October over 200 billion units were produced,—in one month well over ten times the total production of all of last year, yet the total product weighed not much more than ten avoirdupois pounds.

Release

At present most of the material available is supplied directly to the armed services, but for the past seven months limited amounts of penicillin have been released for domestic civilian use and small quantities for urgent foreign needs. During the months prior to April of 1944 small quantities of penicillin had been allocated by the War Production Board to the Office of Scientific Research and Development for a program of clinical research under the direction of Dr. Chester Keefer of Boston.

On May 1, 1944, the War Production Board had available a small surplus of penicillin, over and above military and research

requirements, and under the direction of the Drugs and Cosmetics Branch and the Penicillin Producers' Industry Advisory Committee, a program of allocation for civilian hospitals was inaugurated. The Office of Civilian Penicillin Distribution of the War Production Board was organized by the writer as director, and was located in Chicago. A limited supply of penicillin was released for use in accordance with the recommendations formulated on the basis of the clinical experience by OSRD and NRC workers. The method was to distribute to over 1,000 selected hospitals serving as "depots" in the United States, Alaska, Puerto Rico, Hawaii and the Virgin Islands. These received "quotas" for each month, and from this supplied their own needs and those of the nearby hospitals and practitioners. Now the list has been expanded to include over 2,700 "depot" hospitals.

The first six months of operation of the Office of Civilian Penicillin Distribution saw slightly increasing quantities released each month—a total of over 100 billion Oxford units in the period from May to October, inclusive.

The cost of penicillin, when first quoted, was $20 per vial of 100,000 units, and that acknowledged to be far below actual cost. Now it reaches the civilian hospital at $2.40 per vial, and is supplied to the armed services at less than $1 per vial of 100,000 units each. No doubt the price will go much lower as the present production goals are neared.

Conclusion

Today penicillin is an accepted essential in the armamentarium of *materia medica* of the physicians in America. Perhaps soon the cessation of hostilities in Europe may cause a diminution of requirements for the armed services, and the coming expansion in production may together make possible a supply of penicillin sufficient to permit discontinuance of the present strict control.

The search for newer and better therapeutic agents in the field of antibiotics continues unceasingly. From the research laboratories and manufacturing plants of American pharmaceutical and chemical industry has come an amazing record of achievement which ranks with the great scientific and industrial advances of all time in the history of the United States and of the world. It has been an unsurpassed contribution to the healing professions and to the welfare of mankind.

THE MARTINDALE HERBARIUM

Fifty Years in the Possession of the Philadelphia College of Pharmacy and Science*

By Theodor Philipp Haas, Ph. D.

ON April 3, 1944, it was just half a century since the Philadelphia College of Pharmacy and Science came into the possession of the Martindale Herbarium. This herbarium was presented to the college by Howard B. French and Smith, Kline & French Co. of Philadelphia.

The Martindale Herbarium was one of the most comprehensive private collections in this country, and the Philadelphia College of Pharmacy and Science is keenly aware of its significance and worth. The Biology Department with the cooperation of the President and Dean is making a determined effort to preserve this precious gift and to utilize fully the splendid opportunities it affords.

The Martindale Herbarium was described in the AMERICAN JOURNAL OF PHARMACY, vol. 66, No. 5, May 1894, by George M. Beringer, A. M., Ph. G.; in the book *The Botanists of Philadelphia and Their Work;* by John W. Harshberger, Philadelphia, 1899; and finally in the AMERICAN JOURNAL OF PHARMACY, vol. 103, No. 2, February 1931, there is a shorter article under "Medical and Pharmaceutical Notes," entitled "An Unusual Herbarium," by Dr. M. S. Dunn, the present head of the Department of Biology of the college, who is in charge of the preservation of the Martindale Collection. The latter articles contain information obtained from the first one by Beringer.

Illustration No. 1 shows *Isaac C. Martindale* (by courtesy of the Academy of Natural Sciences in Philadelphia).

The writer of these lines, the last pupil of K. v. Goebel, the famous plant morphologist, was at one time assistant curator of the botanical exhibits of the Botanical Museum in Munich-Nymphenburg. He now has the privilege of doing laboratory work on the Martindale Herbarium. He wishes to use this opportunity to tell something of the technical side of this plant collection.

* The illustrations were made by MR. A. D. WARDEN in the photographic Department of the Academy of Natural Sciences in Philadelphia, Pa.

1842—1893
No. 1. ISAAC C. MARTINDALE (by courtesy of the *Academy of Natural Sciences in Philadelphia*).

Martindale spent a tremendous amount of work and money to build up this large herbarium of many thousand specimens. Beringer estimated that it has a value of $15,000. The nine beautiful wooden cases which contain the Martindale Herbarium, and which Beringer mentions, are decorative indeed, although improvements in housing facilities might be accomplished by substituting dust-tight steel cases in which the fascicles might not be pressed too tightly. We are facing the situation as it is and hope only that later, when the war is over, a way will be found to obtain the right metal cases. In the meanwhile everything possible is being done to keep the sheets free from dust and dirt.

As already stated, the Martindale Herbarium is a very comprehensive collection of plants. The sheets are filed in alphabetical sequence of species within the genera. Sometimes each species is enclosed by a species-cover of white paper. This happens mostly

when several specimens are present. Upon the outside of these species-covers very often are glued clippings from an identification book, the origin of which we don't know. There are also pieces of pages from Asa Gray's *Manual of Botany,* 5th edition (1867). The different species are united within each genus, and enclosed by a genus-cover of a light brown stiff Manila paper. The size of the sheets is larger than is used in general in other collections.

Martindale purchased entire collections—for instance, in 1861 the Ferdinand Rugel Collection. In July, 1874, he bought in Interlaken, Switzerland, the Brunner Collection. There are still in existence booklets and notices, written by Martindale, concerning the purchasing of these collections. Martindale remounted the specimens of the purchased collections and glued their labels upon the new sheets. These labels are often very interesting as they show that the Martindale Herbarium contains plants widely over the world. Among the collectors we find sometimes famous names like St. Hilaire, Schimper, Rusby, and others.

Among others I found the following labels:

C. G. Thedenius, Stockholm;

Ex Museo botanico Holmiensi, communicavit N. J. Andersson (both are from Stockholm, Sweden, with North European plants);

W. Steinitz, Budapest (with Hungarian plants);

Herbier de Ad. Chatin;

Herbier I. E. Planchon (sometimes with signatures of Auguste de St. Hilaire, from the years 1846-47; both with plants from France and West Europe);

Flore des Environs de Rosenlaui, Faulhorn, Grimsel, Furca, etc., ex Collection J. Brunner (with Alpine plants);

Ex Herb. Postian. apud Colleg. Syriens. Protest., Beirut (by George W. Post, author of "Flora of Palestine");

Herbarium Dr. Ferdinand Rugel of Tennessee (sometimes with signatures of Schimper, from 1835-36, concerning Arabian plants, or Endres, dated from the twenties of the 19th century, written in the German language, with plants from Germany);

Mexican Flora, collected by Dr. Edward Palmer;

Flora of New Mexico and Arizona, leg. Henry H. Rusby;

C. G. Pringle, Plantæ Mexicanæ.

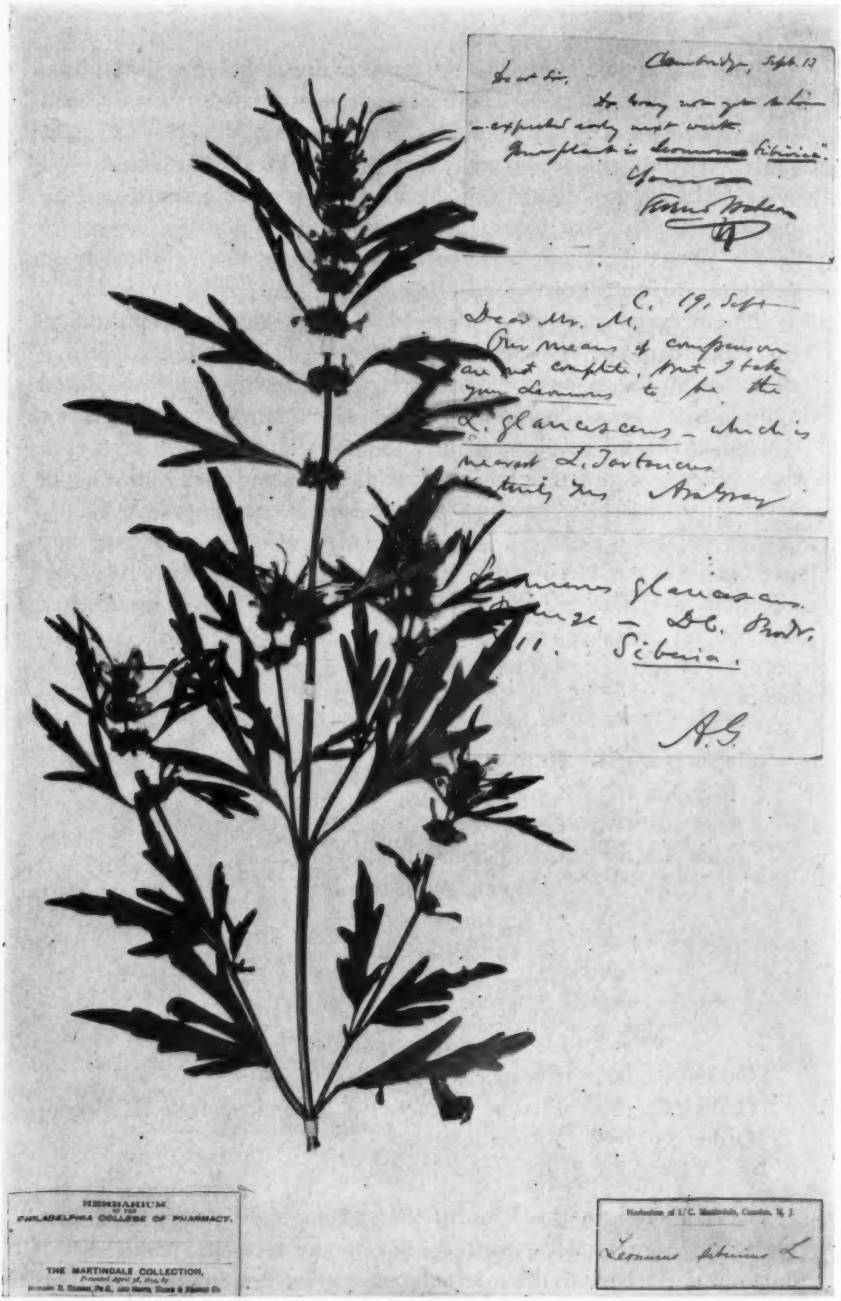
The Martindale Herbarium contains many plants from California, Texas and other States. There are specimens from Australia and New Zealand. The Martindale Collection includes also a great number of fruits and seeds, contained in white cardboard boxes.

Martindale was in correspondence with famous botanists. Frequently he asked Asa Gray (1810-1888), in Cambridge, Mass., to identify plants. Sometimes the answer he received was glued upon the sheet. (Illustration No. 2.)

The arrangement of the Martindale Herbarium follows the system of Bentham and Hooker (Genera Plantarum, 1862-1883). Every family has an index, written on a sheet of pasteboard, which is placed in the shelf where the family starts. Each family has an "order number," assigned to the system of Bentham and Hooker, and each genus bears a sequence number within the family. Each genus cover carries in the left-hand corner a printed label containing name, family number and genus number . The system of Bentham and Hooker may have been most modern at the time when Martindale established his collection, but does not conform to our present knowledge. Most striking, for instance, is that Bentham and Hooker place Gymnospermæ between Dicots and Monocots. There is the following sequence:

Order No. 162.	Empetraceæ	(Angiospermæ, Dicot)
Order No. 163.	Ceratophyllaceæ	(" ")
Order No. 164.	Gnetaceæ	(Gymnospermæ)
Order No. 165.	Coniferæ with the following genus numbers (among others):	
	No. 13. Taxus, Linn.	"
	No. 14. Torreya, Arn.	"
	No. 15. Ginkgo, Linn. (!)	"
	No. 16. Phyllocladus, Rich.	"
Order No. 166.	Cycadaceæ	(")
Order No. 167.	Hydrocharitaceæ ...	(Angiospermæ, Monocot)
Order No. 168.	Burmanniaceæ	(" ")

Even though in this country the system of Engler is used as a rule in museums and in teaching, due to the historical value of the Martindale Herbarium the original arrangement is being left.



No. 2. A sheet of the Martindale Herbarium, with autograms of Asa Gray and Watson, both in Cambridge, Mass.

Following Engler's *Syllabus der Pflanzenfamilien,* 11th edition, 1936, by Diels, we find in the *Encyclopedia Americana,* edition 1942, an arrangement which differs very much from the above-described one. The Gymnospermæ are separated from the Angiospermæ and placed before the latter. That in the Engler system today the Monocots still occur before the Dicots cannot satisfy us, but this system is worked out so completely that we have to take it as it is, without any regard for the fact that we now believe that the Monocots arose from the Dicots, and hence are to be placed after the latter and not before them.

In order to harmonize the arrangement of the Martindale Herbarium with the Engler system and to make its use more practical, we glue upon each genus-cover, near the other labels, a label with the number of the Engler system. We obtain this number from *Genera Siphonogamarum ad Systema Englerianum conscripta ab Auctoribus Dr. C. G. Dalla Torre et Dr. H. Harms,* Leipzig, 1900-1907.

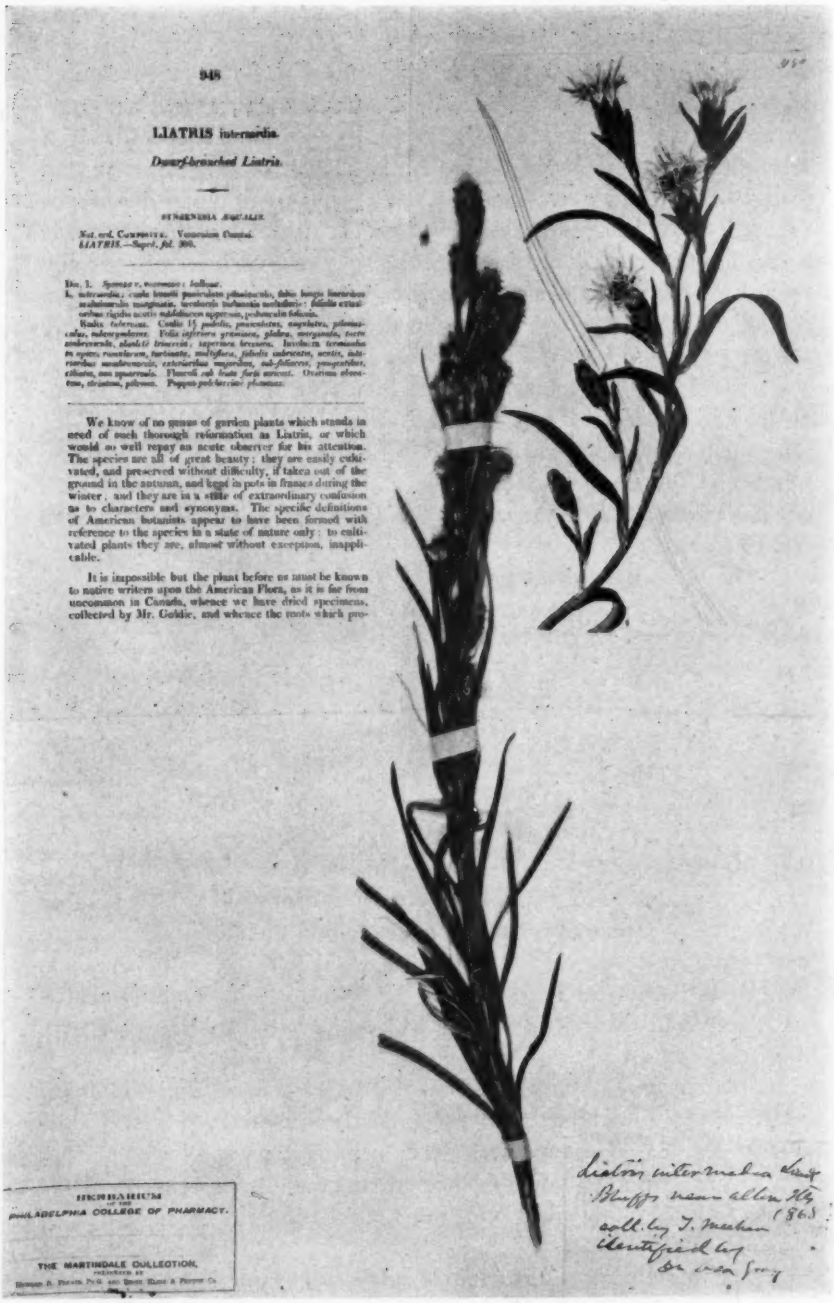
The following is an example:

24	*Tamariscineæ*	*Engler:*
	Tamarix, Linn.	Tamarix No. 5239
	Order No. 24	
	1.	
	Myricaria, Desc.	*Engler:*
	Order No. 24	Myricaria No. 5240
	2.	

The "Order No. 24" is the number in the system of Bentham and Hooker, assigned to the Tamariscineæ (Tamarisks), the number below (1., 2.), the number of the genus within the family. The numbers 5239 and 5240 respectively correspond with the same numbers in the Herbarium of the Academy of Natural Sciences in Philadelphia, and in this way it is very easy to compare the specimens in both herbaria.

In some cases Martindale removed pages of the *Curtis Botanical Magazine* (also with pictures) and glued them upon the sheets. (Illustration No. 3.) This practice is very helpful when specimens are not available. The Martindale Collection contains also specimens of the lower orders of the plant kingdom, but as yet no arrangement of these has been made.

The Martindale Herbarium displays many interesting features, some of which will now be described.


948
LIATRIS intermedia.
Dwarf-branched Liatris.
SYNGENESIA AEQUALIS.
Nat. ord. COMPOSITÆ. Vernonieæ Cassini.
LIATRIS.—Supra, fol. 300.
We know of no genus of garden plants which stands in need of such thorough reformation as Liatris, or which would so well repay an acute observer for his attention. The species are all of great beauty; they are easily cultivated, and preserved without difficulty, if taken out of the ground in the autumn, and kept in pots in frames during the winter, and they are in a state of extraordinary confusion as to characters and synonyms. The specific definitions of American botanists appear to have been formed with reference to the species in a state of nature only: to cultivated plants they are, almost without exception, inapplicable.
It is impossible but the plant before us must be known to native writers upon the American Flora, as it is far from uncommon in Canada, whence we have dried specimens, collected by Mr. Goldie, and whence the roots which pro-
HERBARIUM
OF THE
PHILADELPHIA COLLEGE OF PHARMACY.
THE MARTINDALE COLLECTION.
dialis intermedia Gray
Bluffs near Alton Ill.
coll. by J. Meehan (86)
identified by
Dr Asa Gray

No. 3. A sheet with a page of *Curtis Botanical Magazine* and an autogram of Asa Gray.

Very interesting are the specimens of carnivorous plants, also known as "insectivores." The fact that plants take animal food is one of the most amazing chapters in botany. The methods by which plants catch their prey are different. Some catch the insects with pitcher leaves, acting as a trap into which the prey falls; others do it with sticky hairs; and others have leaves which close like valves and press the insect to death. In the herbarium are huge specimens of the Californian pitcher plant *Darlingtonia californica Torrey;* there are specimens of *Pinguicula, of Drosera, Utricularia,* and, of course, *Dionæa muscipula L.,* the Venus Fly Trap. All these plants were collected in the natural habitat.

Another fact which the Martindale Herbarium shows very well is the similarity of plants which are not at all related to each other. Resemblance in flowers is not a too rare occurrence, for example, the similarity between the flower of the *Papilionaceæ* (the pea family) and the flower of the *Polygalaceæ* (milkwort family). Even more striking is the similarity of entire plants. We see this in succulent plants which store water in their leaves or shoots. Many Aloe and Agave species look very much alike, and the same occurs with cacti and succulent Euphorbia species; the latter are members of the Spurge family. Aloe plants and succulent Euphorbias grow in South Africa; the Agave plants and the cacti grow in the Western Hemisphere under similar conditions. The similarity of their shape is only an adaptation to the surrounding in which they are livng. "Convergence" is the name applied to this parallelism between unrelated plants belonging to different families. It is very surprising indeed when a member of the Knotweed family (*Polygonaceæ*)—its name is *Eriogonum compositum Dougl.,* native in the State of Washington—looks like a carrot, *Daucus carota,* a member of the *Umbelliferæ*. Desert plants in the whole world have similar adaptations for protection against the loss of water. One of these is a dense hair cover on stem and leaf. The air between the hairs is a splendid insulator. Desert plants from Syria and Palestine (Herb. Postian apud College Syriens. Protest. Beirut) show a strong resemblance to plants growing under similar conditions in Arizona or Mexico. These plants, too, possess a rather dense hair cover.

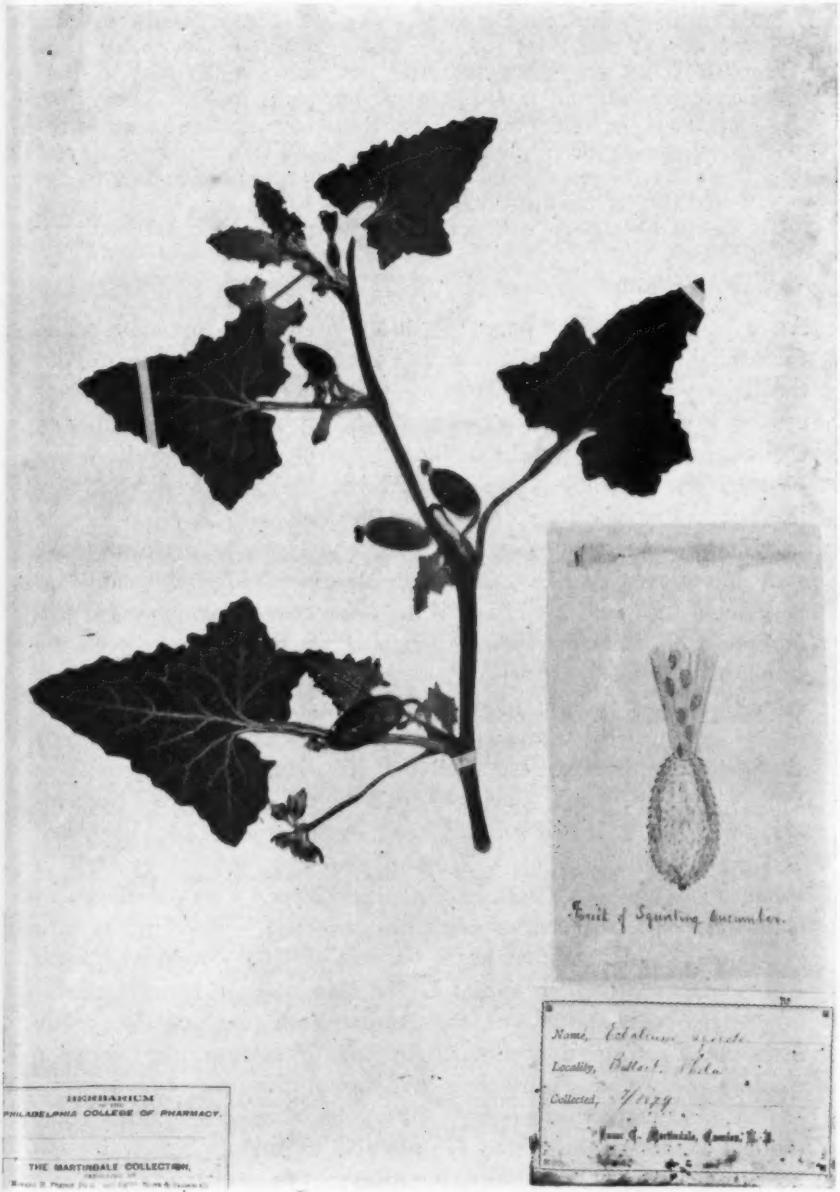
On many sheets in the Martindale Herbarium we find the label "Ballast," mostly "Ballast N. J." This is accounted for by one of the most amazing stories, which is worth relating. There is also lit-

erature of the time of Martindale, and we shall quote the notes in the different articles which deal with this problem.

It is well known that in earlier times ships contained sand and dirt of the lands from whence they came. The sand and dirt was taken from grounds around the shipyards or harbors and served as ballast to increase the stability during the voyage. Columbus is known to have used sand as ballast on his first journey to the Western Hemisphere. Sand-ballast-containing ships came to Philadelphia, Camden, N. J., New York City, Boston, and other seaports of this country. Such ships came to Philadelphia and Camden during the Civil War—the time of Martindale—and during World War I. In this country the sand ballast was thrown out on certain places in the vicinity of Philadelphia and Camden, New York, Boston, and other ports. These places were called "ballast-grounds." On their way back the vessels took food and machines in the place of ballast. In the sand and dirt were contained fruits, seeds, roots and rhizomes of plants from the countries where the dirt was obtained. These plants found favorable conditions around Philadelphia and in other places and began to grow. In this way on the "ballast-grounds" developed a "ballast-flora" with "ballast-plants"—weeds indeed—growing only on the spots where the ballast-dirt was thrown out. Also in World War II sand-ballast-containing ships have again come to Philadelphia and Camden. They are now exclusively from Russia. The curator in charge of the Academy of Natural Sciences in Philadelphia told the writer that he was not able to find out where in Philadelphia the Russian sand-ballast is deposited. The ballast-grounds of the time of Martindale and even of World War I are not used any more, and probably partly covered by streets of the cities of Philadelphia and Camden respectively. (Illustration No. 4.)

The ballast-plants are really adventive plants; this means unintentionally introduced foreign plants. They are weeds from foreign countries. Adventive plants will be found mostly along railroads, around railroad stations and harbors, but they also occur in factories which introduce natural products, like wool, dye wood, etc., from foreign countries. International exhibits also bring such plants to us. With the illustrated sheet of *Leonurus Siberica Bunge* (Illustration No. 2), Martindale writes (*Botanical Gazette,* vol. 2, November, 1876, No. 1, p. 58):

> ". . . I collected near the Wissahickon Station, on the Philadelphia & Reading Railroad, about four miles from Philadelphia,



No. 4. A sheet with a "Ballast Plant," found in the "Ballastground" of Philadelphia. *Ecballium Elaterium A. Rich.* (= Ecballium agreste Reichb.).

> Leonurus glaucescens Bauge.* This plant is from Northern Asia, and how it could get into the above locality is somewhat of a mystery, as no ballast material has been transported to that neighborhood, and it is not a garden plant in this country, at least; it is possible, however, that the seeds may have been introduced among the exhibits to the Centennial Exposition by way of Japan. It is very abundant this year (September 12, 1876), in the locality above mentioned, and seeds have fully ripened, but it remains to be seen whether it will reproduce itself another year or not."
>
> * [Bauge = Bunge?]

As far as we know the plant has disappeared since that time. The Centennial Exposition in Fairmount Park in Philadelphia also brought the Japanese Honeysuckle, *Lonicera japonica L.*, now very abundant around Philadelphia, which has established itself here and farther to the South. It seems to be distributed by birds eating the fruits. The plant has the tendency to migrate southward. Around New York City it is not so abundant by far as around Philadelphia.

The following examples may show how easily ballast-plants may grow in our area. We have in Philadelphia such "adventive plants" as very annoying weeds. Every gardener knows for instance, the garden- or crab-grass *Eleusine indica L.*, which we find even between the stones of Philadelphia streets. How many people realize that this grass came from East India? Among the weeds are many plants which are to be found over the whole world; they are cosmopolites. The weeds are really an "international society!" The conditions of growth in Philadelphia in summer, during the second half of May until September, are so favorable that it is possible to raise tropical plants outdoors. The tropical sensitive plant *Mimosa pudica L.* grew very well in summer 1943 in our "Kilmer Botanical Garden," and seedlings of plants of last year filled a whole bed in 1944. They produced a great quantity of seeds for 1945! In 1944 we have *Zingiber officinale Rosc.*, Ginger, *Mangifera indica L.*, the Mango—raised from a seed—*Cinchona Ledgeriana Moens*, the Quinine-Bark tree, and *Gossypium hirsutum L.*, Cotton, outdoors. In fall, of course, the situation changes and we have to remove our tropical plants.

A great number of adventive plants die in autumn. If they come too late to bloom, and if they are not able to produce ripe fruits and seeds, then these "foreigners" disappear. These latter facts were observed by Martindale and his contemporaries. He was interested greatly in the problem of the adventive plants and wrote several arti-

cles concerning it. Martindale was very active in collecting ballast-plants, even during the Civil War! His specimens are in our Martindale Herbarium.

Now follow in chronological sequence different articles, or extracts of them, written by Martindale himself or by his contemporaries. They all contain lists of ballast-plants. We find also such a list in *Preliminary Catalogue of the Flora of New Jersey, Appendix II.* (See below.)

In two articles published in 1876 and 1879 Martindale refers to an earlier article of *Aubrey H. Smith:* "On Colonies of Plants, observed near Philadelphia," published in the *Proceedings of the Academy of Natural Sciences,* vol. VIX, 1867. Smith writes on pages 15-17:

> ". . . During the years 1864, 1865, and 1866, a large number of introduced plants, chiefly southern, were found growing on the waste grounds below the Philadelphia Navy Yard, and Kaighn's Point and at Petty's Island, on the opposite shore of the Delaware. . . . Nearly opposite the Ballast Ground, on the New Jersey side of the river at Kaighn's Point, is a large enclosed ship and timber yard. . . . Petty's Island is a tract of alluvion on the New Jersey side of the Delaware, opposite the mouth of Cooper's Creek. . . . The Ballast Ground locality was discovered by Messrs. Diffenbaugh and Parker in the latter part of the season 1864; that of Kaghn's Point was made known about the same time by the last named gentleman. Since then the plants of those places, and in 1866 those of Petty's Island, have been carefully watched and collected by a number of botanists. Among these I may especially mention Dr. Martindale, and Messrs. Burk, Diffenbaugh and Parker. All these plants have been submitted to Prof. T. C. Porter, and the determination in all cases of difficulty have his full concurrence. Dr. Porter himself shared the work of collection. . . . It will be observed in many instances that the fruit has not matured, and in some that not even the flower has appeared. . . . A small number of the plants of 1864 did not re-appear in 1865, and some of those of 1865 were not found in 1866."

Smith collected 106 different species in 1867; the plants came mainly from Florida and North Carolina and from Europe. Parker was a friend of Martindale and appears often among the collectors in the Martindale Herbarium.

Martindale writes in the *Botanical Gazette,* vol. II, No. 1, p. 56, November, 1876, in his article "The Introduction of Foreign Plants," after having described the different ways of dispersion of plants:

> ". . . The arrival at the various seaport towns on the coast of ships with ballast from different parts of the world has probably done the greatest work in this introduction and distribution, and it is one which will continue so long as our country can furnish materials to satisfy the wants of other nations. At the port of Philadelphia this has been on a gradual increase for several years, and, as a natural consequence many plants have been collected which probably have not been found elsewhere in the United States."

After these lines by Martindale there follows a list of "Ballast-Plants," that are now contained in the Martindale Herbarium.

Martindale writes in the *Bulletin of the Torrey Botanical Club,* vol. VI, p. 331, August 18, 1879:

> "The introduction of foreign plants in ballast deposits, both here and at Philadelphia, still continues. I have collected more new arrivals this year than for some time past. They are chiefly of species from Southern Europe (The Martindale Herbarium contains, for instance, *Ecballium Elaterium A. Rich.* from the Mediterranean; Ill. No. 4!), some from the African coast and occasionally some from the West Indies and South America."

The short notice of September, 1876, concerning *Leonurus glaucescens* has already been mentioned.

Martindale has also collected in Communipaw and Hoboken, N. J. In the book above-mentioned *A. Preliminary Catalogue of the Flora of New Jersey,* compiled by *N. L. Britton,* Ph. D., Appendix II, p. 128, Office of the Survey, Rutgers College, New Brunswick, N. J., 1881, is contained a list of plants, mostly of European origin, found on ballast deposits at Camden and in the vicinity of New York City (Communipaw and Hoboken). Among the 260 different specimens which were found, Martindale is mentioned eighteen times as collector.

The Martindale Herbarium is no mere collection of dead plants; the work of Martindale is still alive today. We use the Martindale Herbarium very much in our class work in taxonomy, general botany, and also in our special plant demonstrations. Visitors come to us in order to identify plants or to get information. So, the life work of Isaac C. Martindale, half a century ago, serves still for teaching and research, and it will be of great value for the education of future generations.

SELECTED ABSTRACTS

Penicillin Cream. M. H. Payne. *Pharm. J. 99,* 133 (1944). A satisfactory method for the preparation of penicillin creams containing 30 per cent of Lanette wax SX in distilled water is described. It was found necessary to use glass utensils and water distilled from glass apparatus, since a batch of cream prepared in a copper steam-pan lost its activity in three days.

The chopped wax is melted in a 2-liter flask on a water-bath, and to it is slowly added boiling distilled water, shaking well after each addition. The resulting product can then be poured directly into sterile jars counter-balanced on the scales, after which it is treated as described below.

Wide-mouthed, screw-cap jars of 4 oz. size, and without shoulder constriction, are used. The caps should preferably be of heat-resisting bakelite; if of metal, the interior is coated with petrolatum to prevent rusting. Through the cap at a distance of one-fourth of an inch from the periphery is drilled a hole of a size just sufficient to admit a No. 16 gauge hypodermic needle. The jars and caps are heated for one hour at 150° C. in a hot-air sterilizer.

Rubber washers which are cut to fit exactly the inside of the cap are used, and should be boiled for a few minutes before use.

Forty-eight grams of the liquid cream are weighed into each jar, a piece of cellophane is pressed down over the top, and then the cap (with a washer) is screwed on quite tightly. The puncture and the edge of the lid are sealed with waterproof adhesive tape. The jars are then autoclaved at 20 lb. for 20-30 minutes, reducing the pressure gradually before opening the autoclave. The jars are removed while hot and are rotated gently to avoid separation of the contents. When congelation begins the jars are immersed to two-thirds of their height in a water-bath at 70° C., and after ten minutes the cream will have just liquefied.

The adhesive tape is then removed from the puncture in the cap, and by means of a sterile syringe and needle 2 mils of a sterile solution of penicillin containing the desired number of units (usually 10,000, equivalent to 200 units per gram of cream) are injected through the rubber washer. The jar is removed from the water-bath, shaken vigorously for a minute, and then removed to a cool place or refrig-

erator. Finally, each puncture is closed with tape; after labeling and dating, the jar is wrapped in cellophane.

It is emphasized that the directions for autoclaving be observed, since it was found that a sterile product could not be obtained by autoclaving the cream at 10 lb. for one hour.

Water Incorporated Ointment Bases. M. Mandleberg. *Pharm. J. 99,* 143 (1944). A shortage of soft paraffin led the author to devise an ointment base for use in the dispensary of a British medical unit stationed in North Africa. Clinical trials of the product were completely satisfactory.

The base consisted of a stable W/O emulsion containing 55 per cent of water; it was found to withstand extremes of temperature and aging. Whenever soft paraffin was available in sufficient quantity, 25 per cent of this ingredient was incorporated, giving a product with a water content of approximately 41 per cent. The formula for the base is as follows:

Wool fat	5 gm.
Soft paraffin	5 gm.
Liquid paraffin	10 gm.
Hard paraffin	15 gm.
Lanette wax SX	10 gm.
Water	55 mils.

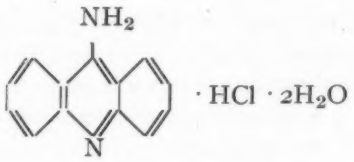
A low and steady heat should be employed in melting the ingredients; in particular, overheating or boiling the Lanette wax must be avoided. The two phases of the emulsion should be at approximately equal temperatures. Emulsification is secured by adding the aqueous phase wholly to the oil phase, and by constant but not too vigorous trituration.

This ointment base was used in the preparation of Dilute Ointment of Ammoniated Mercury, Compound Ointment of Benzoic Acid, and Sulfanilamide Ointment, the water content of which was, respectively, 75 per cent, 34 per cent, and 18.6 per cent.

From clinical observations it is believed that the inclusion of water in an ointment resulted in a readier absorption by the skin of some medicaments.

5-Aminoacridine Hydrochloride: Some Pharmaceutical and Chemical Properties. J. E. Falk and N. M. Thomas. *Pharm J. 99,* 158 (1944). Clinical observations have established the advantage of 5-aminoacridine hydrochloride as an antiseptic over other members of the acridine series which cause stains and which are less stable.

The compound usually is marketed as the dihydrate, the structural formula of which is as follows:



The dihydrate occurs as a pale yellow, crystalline, bitter-tasting, odorless powder. It is soluble in less than 10 parts of boiling water, or in about 300 parts of water at 18° C. At 18° C. one gram of the dihydrate is soluble in 158 mils of 90 per cent alcohol, in 5.5 mils of glycerin, and in 1000 parts of semi-isotonic saline solution. A saturated solution is pale yellow in color and has a moderately intense greenish-blue fluorescence; a 1 : 10,000 solution exhibits a powerful violet blue fluorescence. An aqueous solution is stable to light and it does not stain the skin or fabrics, since it may easily be removed by water.

The melting point of the free base is 241° C. (corr.) with a permissible tolerance of —2° C.

An aqueous solution of 5-aminoacridine hydrochloride has pH6 ± 0.5. The addition of a very small amount of alkali brings the pH above 8, and since the free base is but slightly soluble it will precipitate. The hydochloride is readily salted out from solution by salts and acids.

Studies on the stability toward sunlight of 1 : 1000 solutions of 5-aminoacridine hydrochloride, 2,7-diaminoacridine hydrochloride, and proflavine sulfate B. P. After exposure of the solutions to light the free bases were obtained by precipitation with alkali, and the melting points were then recorded. It was found that the 5-aminoacridine hydrochloride solution was not affected by as much as 30 days' exposure to light, whereas the other solutions showed decomposition after one day's exposure.

Heating 5-aminoacridine hydrochloride dihydrate at 150° C. for one hour caused it to lose water but did not otherwise change it. The 1 : 1000 solution was found to be unchanged after autoclaving at 120° C. for half an hour.

The hydrochloride may be mixed in all proportions with sulfonamides. It is compatible in all concentrations with a 2 per cent solution of butethanol, and at 1 : 1000 strength with the B. P. solution of adrenalin hydrochloride, solution of ephedrine hydrochloride 1 : 1000, solution of procaine hydrochloride 5 per cent, solution of zinc sulfate 1 per cent, and acetic acid 2 per cent. It is incompatible with sodium carbonate, sodium benzoate, with acids and alkalis in general, and (except when in very low concentrations) with all chlorides.

An isotonic 1 : 1000 solution of pH 6.8 may be prepared by dissolving 0.1 gm. of the hydrochloride, 0.05 gm. of borax, 1.2 gm. of boric acid, and 0.3 gm. of sodium chloride in sufficient water to make 100 mils.

Effect of Sodium Perborate upon the Gingival Mucosa: A Controlled Experiment. I. Glickman and B. G. Bibby. *J. A. D. A. 31,* 1201 (1944). A correlated clinical and histologic study was conducted upon five adult dogs to determine (a) whether repeated treatment with unflavored sodium perborate, flavored sodium perborate and neutralized sodium perborate ("neutrox") caused changes in the gingival mucosa and (b) the nature of such changes.

Pastes were prepared containing 4.5 parts by weight of a glucose syrup and one part of each of the three types of sodium perborate. Control pastes containing (1) precipitated calcium carbonate instead of a treatment drug or (2) sodium hydroxide, with a pH of approximately 10, were also used. In order to study the extent to which alkalinity produces changes in the mucosa, a 1 per cent W/V solution of calcium metaphosphate having a pH of 3.1 was used as a wash after the treatment.

Cotton rolls covered with a thick layer of prepared paste were held in apposition with the gingival mucosa in selected quadrants for five minutes in four of the animals or three minutes in the remaining

one. Immediately following treatment the areas were irrigated with either water or the calcium metaphosphate solution.

At the outset of the experiment all animals exhibited a slight marginal gingivitis with erythema and edema. This condition persisted throughout the investigation and in no instance was there any evidence that the sodium perborate preparations tested had therapeutic value either in altering this state or alleviating the non-specific inflammatory ulceration which resulted from their use. The calcium metaphosphate solution produced no appreciable alteration in the effect of sodium perborate on the gingival mucosa. In all instances repeated sodium perborate treatments aggravated the ulcerations or lesions which were produced by this substance and actually retarded healing. Spontaneous healing occurred in all cases when the drug was disconeinued.

A detailed report of the histologic findings is presented.

•

Relationship Between Gingivitis and Penicillin Administration: Preliminary Report. A. E. Strock. *J. A. D. A. 31,* 1235 (1944). Oral examinations made on 198 patients who were treated with from 80,000 to 9,000,000 units of penicillin for various conditions which included gonorrhea, syphilis, osteomyelitis, septicemia, subacute bacterial endocarditis, and brain abscesses revealed that in all cases the gingivæ were remarkable in tone and free from inflammation. In 37 instances there was a history of ulceration and spontaneous bleeding at the time penicillin therapy was started, or a history of bleeding gums for which treatment had been sought within three months prior to the administration of penicillin.

In an attempt to verify this observation under controlled conditions a study was made of 15 patients with Vincent's infection. No oral hygienic measures such as brushing the teeth or irrigating the mouth were permitted. Penicillin was administered in amounts varying from 1,250,000 units intramuscularly to 5,000 units held in the mouth for lengths of time ranging from one hour to continuous bathing except when eating or sleeping.

Prompt improvement in the gingivæ was noted in all cases. Relief from subjective symptoms occurred within the first twenty-four

hours, followed by obvious clinical progress until healing was complete. The number of oral spirochetes and fusiform bacilli decreased rapidly, and in some cases the organisms could not be recovered after a short period of treatment.

A further investigation including microscopic studies is in progress.

Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1943, with Special Reference to Arsenical Dermatitis. T. J. Carter, W. M. Chambers and L. T. Anderson. *U. S. Med. Bull. 43,* 787 (1944). During 1943 medical officers of the United States Navy administered 245,331 doses of arsenicals; the total number of reactions observed was 48, of which 24 were mild, 23 severe, and 1 fatal.

Mapharsen was the drug of choice, since 227,796 doses of this compound were given. It caused 13 mild and 16 severe reactions. Neoarsphenamine was next in frequency of choice; in the administration of 15,626 doses there were 11 mild reactions, 7 severe, and 1 fatality. No reactions were observed in the administration of 1,611 doses of tryparsamide, 266 of bismarsen, and 32 of sulfarsphenamine.

It is of some interest to note the changing trend in arsenical therapy which is evident from a comparison of the above data with that recorded for the nineteen-year period covering 1925 to 1943. For these years the arsenicals employed were administered in the following decreasing order of frequency; the dates within parentheses indicate the year during which the drug was first used by the Medical Corps of the United States Navy: neoarsphenamine, mapharsen (1935), tryparsamide, arsphenamine, sulfarsphenamine, bismarsen (1929), acetarsone (1932), silver arsphenamine (1931).

The various reactions to arsenical therapy during 1929-43 are classified in tabular form.

Of the 48 reactions observed during 1943, dermatitis in some form was seen in 26 instances, of which 13 were mild and an equal number severe. Fifteen of these 26 cases of arsenical dermatitis followed the administration of mapharsen, and the remainder were caused by neoarsphenamine. Case reports are presented on these patients.

Intravenous Bismuth Therapy. A. P. Hudgins. *Clin. Med. 51,* 277 (1944). The author enumerates several indications other than syphilis for bismuth therapy as reported in the literature; these include Vincent's infection, bronchitis (especially if associated with bronchiectasis or in "post-influenzal" bronchitis), tonsilitis, malaria, juvenile warts, and spirochetal infections of the mouth or throat.

A report is presented on the intravenous administration of 1,200 doses of bismuth sodium tartrate almost exclusively as an antisyphilitic to a series of 100 selected patients over a period of seven years. The drug was used in 3 per cent aqueous solution, the dose being from one to two cc. once or twice a week.

In this series there was occasional nausea but rarely vomiting. The complaint noted most frequently was aching in the jaws and teeth. Holding hot water in the mouth during or following treatment was found to be effective in relieving this discomfort. No toxic reactions of significance were observed.

The advantages claimed for intravenous bismuth therapy over the intramuscular route are that in the former the drug is made more available and more rapid in action and in addition the administration is less painful.

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Ethyl Alcohol 85%	33 cc.
Glycerin	33 cc.

It is best dispensed in screw-capped bottles and it is applied by freely mopping the infected areas and then allowing about five minutes to permit drying. According to the authors more than half the patients treated were completely healed after one application and the rest were healed after two or three treatments at five to seven-day intervals.

BOOK REVIEW

Synopsis of Clinical Laboratory Methods. by W. E. Bray, B. A., M. D. Third Edition. 496 pages, 93 illustrations, 20 color plates. 1944. The C. V. Mosby Company, St. Louis 3, Mo. Price: $5.00.

The form of this small compact manual on laboratory diagnosis is similar to that found in the previous editions. However, the sections on blood and blood transfusion, urinalysis, blood chemistry, bacteriology and intestinal parasites have been enlarged. There also are many new additions in the section on hematology. Its table of contents surveys in the 16 chapters a comprehensive, practical context, containing detailed data which is very informative. Bray's Synopsis of Clinical Laboratory Methods deserves the attention of laboratory workers everywhere, especially those interested in laboratory procedures in relation to disease.

L. G.

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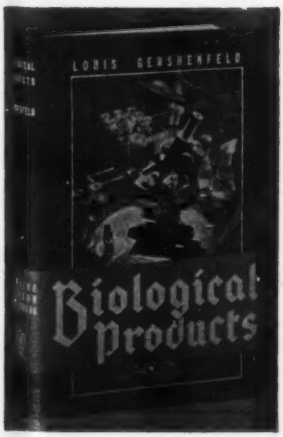

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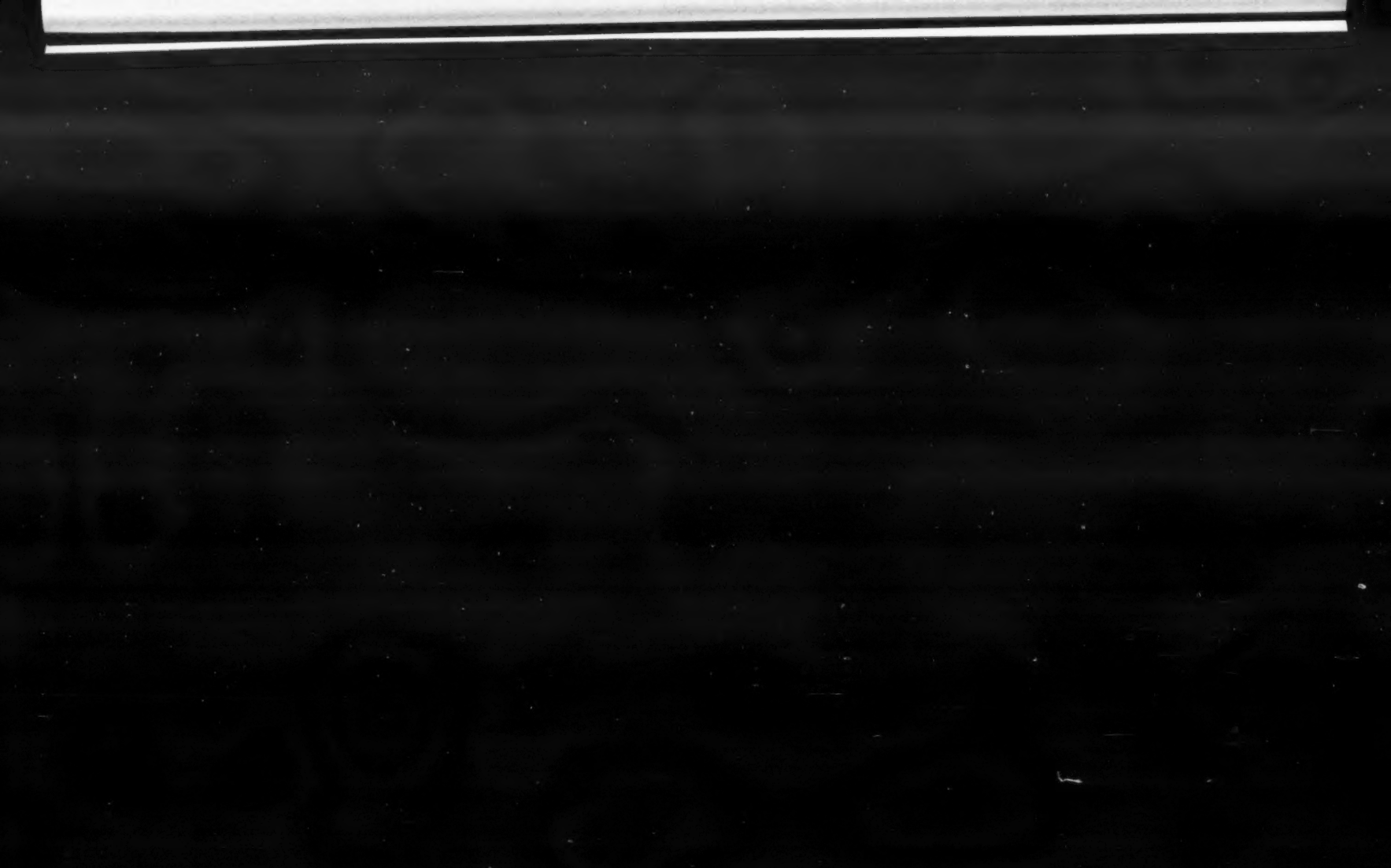

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